

PRESCRIBING INFORMATION

PARNATE®

brand of

**tranylcypromine sulfate
tablets 10 mg**

Before prescribing, the physician should be familiar with the entire contents of this prescribing information.

DESCRIPTION

Chemically, tranylcypromine sulfate is (±)-*trans*-2-phenylcyclopropylamine sulfate (2:1).

Each round, rose-red, film-coated tablet is imprinted with the product name PARNATE and SKF and contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine. Inactive ingredients consist of cellulose, citric acid, croscarmellose sodium, D&C Red No. 7, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, iron oxide, lactose, magnesium stearate, talc, titanium dioxide and trace amounts of other inactive ingredients.

NOTE: Parnate (tranylcypromine sulfate) tablets have been changed from rose-red sugar-coated tablets to rose-red film-coated tablets. The film-coated tablets differ in size from the sugar-coated tablets, but the drug content remains unchanged.

ACTION

Tranylcypromine is a non-hydrazine monoamine oxidase inhibitor with a rapid onset of activity. It increases the concentration of epinephrine, norepinephrine and serotonin in storage sites throughout the nervous system and, in theory, this increased concentration of monoamines in the brain stem is the basis for its antidepressant activity. When tranylcypromine is withdrawn, monoamine oxidase activity is recovered in 3 to 5 days, although the drug is excreted in 24 hours.

INDICATIONS

For the treatment of Major Depressive Episode Without Melancholia.

Parnate (tranylcypromine sulfate) should be used in adult patients who can be closely supervised. It should rarely be the first antidepressant drug given. Rather, the drug is suited for patients who have failed to respond to the drugs more commonly administered for depression.

The effectiveness of *Parnate* has been established in adult outpatients, most of whom had a depressive illness which would correspond to a diagnosis of Major Depressive Episode Without Melancholia. As described in the American Psychiatric Association's Diagnostic and Statistical Manual, third edition (DSM III), Major Depressive Episode implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning and includes at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration and suicidal ideation or attempts.

The effectiveness of *Parnate* in patients who meet the criteria for Major Depressive Episode with Melancholia (endogenous features) has not been established.

SUMMARY OF CONTRAINDICATIONS

Parnate (tranylcypromine sulfate) should not be administered in combination with any of the following: MAO inhibitors or dibenzazepine derivatives; sympathomimetics (including amphetamines); some central nervous system depressants (including narcotics and alcohol); antihypertensive, diuretic, antihistaminic, sedative or anesthetic drugs; bupropion HCl; buspirone HCl; dextromethorphan; cheese or other foods with a high tyramine content; or excessive quantities of caffeine.

Parnate (tranylcypromine sulfate) should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease, hypertension or history of headache.

(For complete discussion of contraindications and warnings, see below.)

CONTRAINDICATIONS

Parnate (tranylcypromine sulfate) is contraindicated:

1. In patients with cerebrovascular defects or cardiovascular disorders

Parnate should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease or hypertension.

2. In the presence of pheochromocytoma

Parnate should not be used in the presence of pheochromocytoma since such tumors secrete pressor substances.

3. In combination with MAO inhibitors or with dibenzazepine-related entities

Parnate (tranylcypromine sulfate) should not be administered together or in rapid succession with other MAO inhibitors or with dibenzazepine-related entities. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations.

In patients being transferred to *Parnate* from another MAO inhibitor or from a dibenzazepine-related entity, allow a medication-free interval of at least a week, then initiate *Parnate* using half the normal starting dosage for at least the first week of therapy. Similarly, at least a week should elapse between the discontinuance of *Parnate* and the administration of another MAO inhibitor or a dibenzazepine-related entity, or the readministration of *Parnate*.

The following list includes some other MAO inhibitors, dibenzazepine-related entities and tricyclic antidepressants, and the companies which market them.

Other MAO Inhibitors

Generic Name
Furazolidone

Trademark

Isocarboxazid

Marplan®

(Oxford Pharm Services)

Pargyline HCl

Pargyline HCl and methylothiazide

Phenelzine sulfate

Nardil®

(Parke-Davis)

Procarbazine HCl

Matulane®

(Sigma Tau)

Dibenzazepine-Related and Other Tricyclics

Generic Name

Amitriptyline HCl

Trademark

Elavil®
(Zeneca)

Perphenazine and amitriptyline HCl

Etrafon®
(Schering)
Triavil®
(Lotus Biochemical)

Clomipramine hydrochloride

Anafranil®
(Geneva)

Desipramine HCl

Norpramin®
(Aventis)

Imipramine HCl

Janimine™
(Geneva)
Tofranil®
(Novartis)

Nortriptyline HCl

(Geneva)
Pamelor®
(Mallinckrodt)

Protriptyline HCl

Vivactil®
(Merck and Co.)

Doxepin HCl

Sinequan.
(Pfizer).

Carbamazepine

Tegretol®
(Novartis)

Cyclobenzaprine HCl

Flexeril®
(Merck and Co.)

Amoxapine

(Geneva)

Maprotiline HCl

(Mylan)

Trimipramine maleate

Surmontil®
(Wyeth-Ayerst Laboratories)

4. In combination with bupropion

The concurrent administration of a MAO inhibitor and bupropion hydrochloride (Wellbutrin®, Wellbutrin SR® Ziban® GlaxoSmithKline) is contraindicated. At least 14 days should elapse between discontinuation of a MAO inhibitor and initiation of treatment with bupropion hydrochloride.

5. In combination with dexfenfluramine hydrochloride

Because dexfenfluramine hydrochloride is a serotonin releaser and reuptake inhibitor, it should not be used concomitantly with Parnate (tranylcypromine sulfate).

6. In combination with selective serotonin reuptake inhibitors (SSRIs)

As a general rule, *Parnate* should not be administered in combination with any SSRI. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine (Prozac, Ely Lilly and Co.) in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine and other SSRIs should not be used in combination with a MAOI, or within 14 days of discontinuing therapy with a MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping fluoxetine before starting a MAOI.

At least 2 weeks should be allowed after stopping sertraline (Zoloft, Pfizer) or paroxetine (Paxil, GlaxoSmithKline) before starting a MAOI.

7. In combination with buspirone

Parnate (tranylcypromine sulfate) should not be used in combination with buspirone HCl (BuSpar®, Bristol-Myers Squibb), since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCl. At least 10 days should elapse between the discontinuation of *Parnate* and the institution of buspirone HCl.

8. In combination with sympathomimetics

Parnate (tranylcypromine sulfate) should not be administered in combination with sympathomimetics, including amphetamines, and over-the-counter drugs such as cold, hay fever or weight-reducing preparations that contain vasoconstrictors.

During *Parnate* therapy, it appears that certain patients are particularly vulnerable to the effects of sympathomimetics when the activity of certain enzymes is inhibited. Use of sympathomimetics and compounds such as guanethidine, methyldopa, reserpine, dopamine, levodopa and tryptophan with *Parnate* may precipitate hypertension, headache and related symptoms. In addition, use with tryptophan may precipitate disorientation, memory impairment and other neurologic and behavioral signs.

9. In combination with meperidine

Do not use meperidine concomitantly with MAO inhibitors or within 2 or 3 weeks following MAOI therapy. Serious reactions have been precipitated with concomitant use, including coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse and death. It is thought that these reactions may be mediated by accumulation of 5-HT (serotonin) consequent to MAO inhibition.

10. In combination with dextromethorphan

The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior.

11. In combination with cheese or other foods with a high tyramine content

Hypertensive crises have sometimes occurred during *Parnate* therapy after ingestion of foods with a high tyramine content. In general, the patient should avoid protein foods in which aging or protein breakdown is used to increase flavor. In particular, patients should be instructed not to take foods such as cheese (particularly strong or aged varieties), sour cream, Chianti wine, sherry, beer (including nonalcoholic beer), liqueurs, pickled herring, anchovies, caviar, liver, canned figs, dried fruits (raisins, prunes, etc.), bananas, raspberries, avocados, overripe fruit, chocolate, soy sauce, sauerkraut, the pods of broad beans (fava beans), yeast extracts, yogurt, meat extracts or meat prepared with tenderizers.

12. In patients undergoing elective surgery

Patients taking *Parnate* should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of *Parnate* and spinal anes-

(continued)

Parnate® (tranylcypromine sulfate) continued

thesia should be kept in mind. *Parnate* should be discontinued at least 10 days prior to elective surgery.

ADDITIONAL CONTRAINDICATIONS

In general, the physician should bear in mind the possibility of a lowered margin of safety when Parnate (tranylcypromine sulfate) is administered in combination with potent drugs.

1. *Parnate* should not be used in combination with some central nervous system depressants such as narcotics and alcohol, or with hypotensive agents. A marked potentiating effect on these classes of drugs has been reported.
2. Anti-parkinsonism drugs should be used with caution in patients receiving *Parnate* since severe reactions have been reported.
3. *Parnate* should not be used in patients with a history of liver disease or in those with abnormal liver function tests.
4. Excessive use of caffeine in any form should be avoided in patients receiving *Parnate*.

WARNING TO PHYSICIANS

Parnate (tranylcypromine sulfate) is a potent agent with the capability of producing serious side effects. *Parnate* is not recommended in those depressive reactions where other antidepressant drugs may be effective. **It should be reserved for patients who can be closely supervised and who have not responded satisfactorily to the drugs more commonly administered for depression.**

Before prescribing, the physician should be completely familiar with the full material on dosage, side effects and contraindications on these pages, with the principles of MAO inhibitor therapy and the side effects of this class of drugs. Also, the physician should be familiar with the symptomatology of mental depressions and alternate methods of treatment to aid in the careful selection of patients for *Parnate* therapy. In depressed patients, the possibility of suicide should always be considered and adequate precautions taken.

Pregnancy Warning: Use of any drug in pregnancy, during lactation or in women of child-bearing age requires that the potential benefits of the drug be weighed against its possible hazards to mother and child.

Animal reproductive studies show that *Parnate* passes through the placental barrier into the fetus of the rat, and into the milk of the lactating dog. The absence of a harmful action of *Parnate* on fertility or on postnatal development by either prenatal treatment or from the milk of treated animals has not been demonstrated. Tranylcypromine is excreted in human milk.

WARNING TO THE PATIENT

Patients should be instructed to report promptly the occurrence of headache or other unusual symptoms, i.e., palpitation and/or tachycardia, a sense of constriction in the throat or chest, sweating, dizziness, neck stiffness, nausea or vomiting.

Patients should be warned against eating the foods listed in Section 11 under Contraindications while on Parnate (tranylcypromine sulfate) therapy. Also, they should be told not to drink alcoholic beverages. The patient should also be warned about the possibility of hypotension and faintness, as well as drowsiness sufficient to impair performance of potentially hazardous tasks such as driving a car or operating machinery.

Patients should also be cautioned not to take concomitant medications, whether prescription or over-the-counter drugs such as cold, hay fever or weight-reducing preparations, without the advice of a physician. They should be advised not to consume excessive amounts of caffeine in any form. Likewise, they should inform other physicians, and their dentist, about their use of *Parnate*.

WARNINGS

HYPERTENSIVE CRISES: The most important reaction associated with Parnate (tranylcypromine sulfate) is the occurrence of hypertensive crises which have sometimes been fatal.

These crises are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea or vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin) and photophobia. Either tachycardia or bradycardia may be present, and associated constricting chest pain and dilated pupils may occur. **Intracranial bleeding, sometimes fatal in outcome, has been reported in association with the paradoxical increase in blood pressure.**

In all patients taking *Parnate* blood pressure should be followed closely to detect evidence of any pressor response. It is emphasized that full reliance should not be placed on blood pressure readings, but that the patient should also be observed frequently.

Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during *Parnate* therapy. These signs may be prodromal of a hypertensive crisis.

Important:

Recommended treatment in hypertensive crises

If a hypertensive crisis occurs, Parnate (tranylcypromine sulfate) should be discontinued and therapy to lower blood pressure should be instituted immediately. Headache tends to abate as blood pressure is lowered. On the basis of present evidence, phentolamine is recommended. (The dosage reported for phentolamine is 5 mg I.V.) Care should be taken to administer this drug slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling. Other symptomatic and supportive measures may be desirable in particular cases. Do not use parenteral reserpine.

PRECAUTIONS

Hypotension

Hypotension has been observed during Parnate (tranylcypromine sulfate) therapy. Symptoms of postural hypotension are seen most commonly but not exclusively in patients with pre-existent hypertension; blood pressure usually returns rapidly to pretreatment levels upon discontinuation of the drug. At doses above 30 mg daily, postural hypotension is a major side effect and may result in syncope. Dosage increases should be made more gradually in patients showing a tendency toward hypotension at the beginning of therapy. Postural hypotension may be relieved by having the patient lie down until blood pressure returns to normal.

Also, when *Parnate* is combined with those phenothiazine derivatives or other compounds known to cause hypotension, the possibility of additive hypotensive effects should be considered.

OTHER PRECAUTIONS

There have been reports of drug dependency in patients using doses of tranylcypromine significantly in excess of the therapeutic range. Some of these patients had a history of previous substance abuse. The following withdrawal symptoms have been reported: restlessness, anxiety, depression, confusion, hallucinations, headache, weakness and diarrhea.

Drugs which lower the seizure threshold, including MAO inhibitors, should not be used with Amipaque®†. As with other MAO inhibitors, Parnate (tranylcypromine sulfate) should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.

In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. Exclusive reliance on drug therapy to prevent suicidal attempts is unwarranted, as there may be a delay in the onset of therapeutic effect or an increase in anxiety and agitation. Also, some patients fail to respond to drug therapy or may respond only temporarily.

MAO inhibitors may have the capacity to suppress anginal pain that would otherwise serve as a warning of myocardial ischemia.

The usual precautions should be observed in patients with impaired renal function since there is a possibility of cumulative effects in such patients.

Older patients may suffer more morbidity than younger patients during and following an episode of hypertension or malignant hyperthermia. Older patients have less compensatory reserve to cope with any serious adverse reaction. Therefore, *Parnate* should be used with caution in the elderly population.

Although excretion of *Parnate* is rapid, inhibition of MAO may persist up to 10 days following discontinuation.

Because the influence of *Parnate* on the convulsive threshold is variable in animal experiments, suitable precautions should be taken if epileptic patients are treated.

Some MAO inhibitors have contributed to hypoglycemic episodes in diabetic patients receiving insulin or oral hypoglycemic agents. Therefore, *Parnate* should be used with caution in diabetics using these drugs.

Parnate may aggravate coexisting symptoms in depression, such as anxiety and agitation.

Use Parnate (tranylcypromine sulfate) with caution in hyperthyroid patients because of their increased sensitivity to pressor amines.

Parnate should be administered with caution to patients receiving Antabuse®†. In a single study, rats given high intraperitoneal doses of *d* or *l* isomers of tranylcypromine sulfate plus disulfiram experienced severe toxicity including convulsions and death. Additional studies in rats given high oral doses of racemic tranylcypromine sulfate (*Parnate*) and disulfiram produced no adverse interaction.

ADVERSE REACTIONS

Overstimulation which may include increased anxiety, agitation and manic symptoms is usually evidence of excessive therapeutic action. Dosage should be reduced, or a phenothiazine tranquilizer should be administered concomitantly.

Patients may experience restlessness or insomnia; may notice some weakness, drowsiness, episodes of dizziness or dry mouth; or may report nausea, diarrhea, abdominal pain or constipation. Most of these effects can be relieved by lowering the dosage or by giving suitable concomitant medication.

Tachycardia, significant anorexia, edema, palpitation, blurred vision, chills and impotence have each been reported.

Headaches without blood pressure elevation have occurred.

Rare instances of hepatitis, skin rash, and alopecia have been reported.

Impaired water excretion compatible with the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) has been reported.

Tinnitus, muscle spasm, tremors, myoclonic jerks, numbness, paresthesia, urinary retention and retarded ejaculation have been reported.

Hematologic disorders including anemia, leukopenia, agranulocytosis and thrombocytopenia have been reported.

Post-Introduction Reports

The following are spontaneously reported adverse events temporally associated with *Parnate* therapy. No clear relationship between *Parnate* and these events has been established. Localized scleroderma, flare-up of cystic acne, ataxia, confusion, disorientation, memory loss, urinary frequency, urinary incontinence, urticaria, fissuring in corner of mouth, akinesia.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted to the requirements of the individual patient. Improvement should be seen within 48 hours to 3 weeks after starting therapy.

The usual effective dosage is 30 mg per day, usually given in divided doses. If there are no signs of improvement after a reasonable period (up to 2 weeks), then the dosage may be increased in 10 mg per day increments at intervals of 1 to 3 weeks; the dosage range may be extended to a maximum of 60 mg per day from the usual 30 mg per day.

OVERDOSAGE

SYMPTOMS: The characteristic symptoms that may be caused by overdosage are usually those described above.

However, an intensification of these symptoms and sometimes severe additional manifestations may be seen, depending on the degree of overdosage and on individual susceptibility. Some patients exhibit insomnia, restlessness and anxiety, progressing in severe cases to agitation, mental confusion and incoherence. Hypotension, dizziness, weakness and drowsiness may occur, progressing in severe cases to extreme dizziness and shock. A few patients have displayed hypertension with severe headache and other symptoms. Rare instances have been reported in which hypertension was accompanied by twitching or myoclonic fibrillation of skeletal muscles with hyperpyrexia, sometimes progressing to generalized rigidity and coma.

TREATMENT: Gastric lavage is helpful if performed early. Treatment should normally consist of general supportive measures, close observation of vital signs and steps to counteract specific symptoms as they occur, since MAO inhibition may persist. The management of hypertensive crises is described under WARNINGS in the HYPERTENSIVE CRISES section.

External cooling is recommended if hyperpyrexia occurs. Barbiturates have been reported to help relieve myoclonic reactions, but frequency of administration should be controlled carefully because Parnate (tranylcypromine sulfate) may prolong barbiturate activity. When hypotension requires treatment, the standard measures for managing circulatory shock should be initiated. If pressor agents are used, the rate of infusion should be regulated by careful observation of the patient because an exaggerated pressor response sometimes occurs in the presence of MAO inhibition. Remember that the toxic effect of *Parnate* may be delayed or prolonged following the last dose of the drug. Therefore, the patient should be closely observed for at least a week. It is not known if tranylcypromine is dialyzable.

HOW SUPPLIED

Parnate is supplied as round, rose-red, film-coated tablets imprinted with the product name PARNATE and SB and contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine, in bottles of 100 with a desiccant, manufactured by Abbott Labs North Chicago IL 60064 10 mg 100's: NDC 0007-4471-20

Store between 15° and 30°C (59° and 86°F).
†metrizamide, Sanofi-Synthelabo Inc
†disulfiram, Wyeth-Ayerst Pharmaceuticals
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Research Triangle Park, NC 27709
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